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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/677,495 | 10/03/2003 | Chun L. Gao | 8124.003.US | 4565 |

7590 09/20/2006

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| EXAMINER | |
|---|---|
| HUMPHREY, DAVID HAROLD | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

XX

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/677,495 | GAO ET AL. |
| | **Examiner** | **Art Unit** |
| | David Humphrey | 1643 |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 28 August 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) 21-37 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 and 20 is/are rejected.

7)☒ Claim(s) 19 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/25/04.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☒ Other: sequence alignment.

## DETAILED ACTION

### *Election/Restriction*

1. Applicants' election of Group I, claims 1-20, with traverse in the reply filed on 08/28/2006 is acknowledged. Applicants' election of the species, PSA, with traverse is also acknowledged.

The traversal is on the grounds that Examiner has not demonstrated that there would be a "serious burden" placed on the Examiner to examine more than one group of claims. Applicants' further argue that Groups I and III are in the same class, and two very closely related subclasses.

Applicants' traversal of the species election is also based on Applicants' belief that the Examiner has not demonstrated "serious burden". Applicants further argue that claims 1-20 are generic to the elected species.

Applicant's traversal has been carefully considered but found not persuasive. While a search of the prior art for one Group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources even if the Groups were placed in the same class and subclass. As presented in the Restriction requirement, Inventions I and III have different method objectives as well as different method steps and parameters. Invention I is drawn to method of detection of prostate cancer in a patient. Invention III is drawn to a method of determining the molecular profile of a prostate cancer cell which involves a plurality of cancer-determinant genes, and obtaining multiple samples which is not required for Invention I.

Invention II is drawn to a product (kit) for the detection of early stage cancer. Therefore, Inventions I, II, and III, are patentably distinct.

Applicants' arguments concerning the species election have also been carefully considered but found not persuasive. Again as stated in the Restriction requirement, the claims are drawn to a method of detecting prostate cancer using separate and distinct gene markers. The genes listed in A-H have separate and distinct structures and function and are therefore patentably distinct. For example, prostate-specific antigen (PSA) is a protein produced by normal prostate cells which participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest amounts of PSA are found in the seminal fluid; some PSA escapes the prostate and can be found in the serum. However, PSMA is expressed in the membrane of prostate epithelial cells and is composed of a short 19 amino acid intra-cellular domain, a 24 amino acid transmembrane domain and a 707 amino acid extra-cellular domain.

Therefore, the restriction requirement between Groups I, II, and III, and the species election is maintained.

2. Claims 1-37 are pending.

Claims 21-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim.

Claims 1-20 are examined on the merits to the extent they read on the elected species, PSA.

### *Specification*

3. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

4. The abstract of the disclosure is objected to because there is an extra "a" in line 4 that should be deleted.

Correction is required. See MPEP § 608.01(b).

### *Claim Objections*

5. Claim 7 is objected to because of the following informalities: there is an extra "n" in the word "immunological". Appropriate correction is required.

Claim 19 is objected to for being drawn to non-elected species of the invention.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2, 3, and 20, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2 and 20 are vague and indefinite for the recitation “sensitivity is at least about 80% or greater” in claim 2 and “sensitivity greater than 80%” in claim 20, line 15. It is unclear what sensitivity is in reference to. The sensitivity could relate to the accuracy of the method to correctly detect prostate cancer. Sensitivity could also refer to the ability of the RT-PCR primers and PCR primers to bind and amplify small amounts of PSA mRNA and cDNA, respectively, in a sample containing a high background of non-cancer cells. Therefore, one of ordinary skill would be unable to determine the metes and bounds of the claimed invention.

b. Claims 3 and 20 are vague and indefinite for the recitation “specificity is at least about 85% or greater” in claim 3 and “specificity greater than 85%” in claim 20, lines 15 and 16. It is unclear what specificity is in reference to. Specificity could relate to the specificity of the PCR primers for PSA. Alternatively, specificity could refer to the ability to detect prostate cancer cells as opposed to other cancer cell types. Therefore, one of ordinary skill in the art would be unable to determine the metes and bounds of the claimed invention.

### *Claim Rejections - 35 USC § 102*

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-6, 11, 12, 14, and 18, are rejected under 35 U.S.C. §102(b) as being anticipated by Croce et al. (US Patent 5,674,682, patented October 7, 1997).

Croce et al. disclose a method for detecting prostate cancer in a patient, wherein the method comprises isolating epithelial cells from a sample of blood from said patient, lysing epithelial cells and isolating nucleic acid, conducting RT-PCR on said isolated nucleic acid using a set of primers, Taq polymerase to synthesize cDNA, conducting PCR on said cDNA using PSA-specific primers and Taq polymerase and detecting amplified PSA gene, see column 3, lines 35-66; column 9, lines 15-67; column 10, lines 1-20. Croce et al. also disclose that the prostate cancer includes sub clinical stage, organ-confined prostate cancer in humans (Stages D0 and D1), see column 8, lines 56-64; column 11, lines 1-15. Croce et al. disclose that the blood sample comprises peripheral blood, see column 11, lines 2-4. Croce et al. disclose primers, for example SEQ ID NO: 9, that contain specific exons of the PSA gene which include instant claimed SEQ ID NO: 2 and SEQ ID NO: 4, see column 3, lines 56-66; column 12, lines 45-55. Croce et al. further disclose PCR primers having 75-85% specificity, see 112, 2nd paragraph rejection above; column 9, lines 33-40. Croce et al. further disclose obtaining a blood sample of approximately 6 mL, see column 9, lines 15 and 16. While Croce et al. do not specifically disclose 5 mL samples, it is the Examiner's position that approximately 6 mL encompasses samples ranging from 5-7 mL.

Thus, the instant invention is anticipated by Croce et al.

10. Claims 1, 4-6, 11, 13, 14, 16, and 18, are rejected under 35 U.S.C. §102(b) as being anticipated by Gao et al. (Urology 53: 714-721, 1999).

Gao et al. disclose a method to detect PSA-expressing prostate cancer cells as low as one cell in 10 million lymphocytes (1 X $10^7$), see Abstract, lines 6-8; page 715, right column, Determination of PCR Sensitivity section, lines 6 and 7. Gao et al. disclose a method utilizing RT-PCR wherein 40.7% had non-organ-confined disease, see Abstract, lines 13-15. Gao et al. further disclose that 26% of the human patients with clinically localized disease (organ confined disease) had positive PSA expression by RT-PCR assay and that a positive result correlated with extraprostatic disease and recurrence, see page 715, lines 12-22. Gao et al. further disclose isolating a sample of blood, see page 714-715, bridging sentence. Gao et al. disclose random hexamer primers, primers specific for PSA, and nested PCR primers, see page 715, right column, RT and PCR section, lines 1-5; page 715, bridging sentence to page 716. Gao et al. disclose PSA overexpression correlates with extraprostatic disease (see page 715, left column, lines 12-16) and the isolation of PSA-expressing cells from peripheral blood of patients, see page 715, left column, lines 8-12.

Thus, the instant invention is anticipated by Gao et al.

### *Claim Rejections - 35 USC § 103*

11. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-6, 11-18, and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Croce et al. (US Patent 5,674,682, patented October 7, 1997) in view of Edelstein et al. (WO 96/21042; international publication date 11 July 1996) and Tso et al. (WO 97/38313; international publication date 16 October 1997).

The teachings of Croce et al. are described supra.

Croce et al. do not teach 80% sensitivity of detecting PSA, the use of hexamers and oligo-dT primers. These deficiencies are made up for by the teachings of Edelstein et al.

Edelstein et al. teach a method for detecting prostate cancer using RT-PCR, wherein the method comprises enhancing the sensitivity of detection limits to more than 100,00 fold and reducing the background, see page 19, lines 5-18. Edelstein et al. teach the use of hexamers for reverse transcriptase reaction and oligo dT primers, see page 22, line 29; page 23, line 3. Edelstein et al. teach the use of PSA specific primers including SEQ ID NO: 8 which reads on claimed SEQ ID NO: 4 and SEQ ID NO: 5 which reads on claimed SEQ ID NO: 1, see page 20, lines 15-23. Edelstein et al. further teach the use of primer sequences that correspond to various regions of the exons of the prostate specific antigen gene. Edelstein et al. do not teach a PSA-specific primer comprised of SEQ ID NO: 3. This deficiency is made up for by the teachings of Tso et al.

Tso et al. teach a PSA-specific probe (SEQ ID NO: 3) that comprises SEQ ID NO: 3, see attached sequence alignment; page 21, lines 2-5, 219-28; page 48, claims 11 and 13. Tso et al. teach that the probes can be used for PCR to identify or detect rare cancer cells, see page 20, lines 15-21.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting PSA expressing cells as taught by Croce et al. to enhance the sensitivity and specificity of detecting PSA using the primers taught by Edelstein et al. and Tso et al. for the purpose of reducing the background noise. One of ordinary skill in the art would have a reasonable expectation of success that the combination of the teachings of Croce et al and Edelstein et al. would provide the advantage of developing a sensitive and an improved system for amplifying target nucleic acid molecules because Edelstein et al. explicitly taught the enhancing sensitivity and specificity of detection of PSA, see page 19, lines 5-18. A person of ordinary skill in the art would have been motivated to combine the method for detecting prostate cancer as taught by Croce et al. by incorporating the step to enhance sensitivity of detection of PSA as taught by Edelstein et al. for the purpose of developing an improved and sensitive system for detecting PSA-expressing cells from a mixture of cells.

Thus, claims 1-6 and 11-18, and 20, are obvious over Croce et al. in view of Edelstein et al. and Tso et al.

13. Claims 1, 3-12, 14, and 18, are rejected under 35 U.S.C. §103(a) as being unpatentable over Croce et al. (US Patent 5,674,682, patented October 7, 1997) in view of Terstappen et al. (US Patent 6,365,362, filed 12 February 1999).

The teachings of Croce et al. are described supra.

Croce et al. do not teach isolating epithelial cells using immunological methods selected from the group consisting of immunoprecipitation, immuno-affinity chromatography, and dynabead enrichment. Croce et al. do not teach the immunological technique comprises antibodies specific to epithelial antigens selected from the group Ber-EP4 antigen, epithelial membrane antigens, epithelial cell-surface antigens. This deficiency is made up for by the teachings of Terstappen et al.

Terstappen et al. teach a method for detection and enrichment of prostate specific cells from blood sample said method comprises use of immunomagnetic beads (dynal magnetic beads) to isolate said cells, see column 8, lines 11-53. Terstappen et al. teach the use of antibodies to epithelial antigens such as anti-EpCAM to enrich or isolate epithelial cells, see column 10, lines 32-37.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting PSA expressing cells as taught by Croce et al. with enrichment of tumor specific cells as taught by Terstappen et al. for the purpose of amplifying tumor specific cells and reducing the background noise. A person of ordinary skill in the art would have been motivated to combine the method for detecting prostate cancer as taught by Croce et al. by incorporating the step to enriching tumor specific cells as taught by Terstappen et al. for the purpose of developing an improved and sensitive system for detecting PSA-expressing cells from a mixture of cells to reduce background noise.

One of ordinary skill in the art would have a reasonable expectation of success that the teachings of Croce et al. and Terstappen et al. would achieve an expected advantage of developing a sensitive and an improved system for amplifying target nucleic acid molecules because Terstappen et al. explicitly taught the enriching circulating tumor specific cells for detection of cancer cells, see column 15, lines 54-67; column 16, lines 1-6.

Thus, claims 1, 3-12, 14, and 18, are obvious over Croce et al. in view of Terstappen et al.

14. Claims 1-6, 11-16, 18, and 20, are rejected under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology 53: 714-721, 1999) in view of Edelstein et al. (WO 96/21042; international publication date 11 July 1996).

The teachings of Gao et al. are described supra.

Gao et al. do not teach 80-85 % sensitivity and specificity of detecting PSA, and the use of oligo-dT primers. These deficiencies are made up for by the teachings of Edelstein et al.

Edelstein et al. teach a method for detecting prostate cancer using RT-PCR, wherein the method comprises enhancing the sensitivity of detection limits to more than 100,00 fold and reducing the background, see page 19, lines 5-18. Edelstein et al. teach the use of hexamers for reverse transcriptase reaction and oligo dT primers, see page 22, line 29; page 23, line 3. Edelstein et al. teach the use of PSA specific primers including SEQ ID NO:8 which reads on claimed SEQ ID NO: 4 and SEQ ID NO: 5 which reads on claimed SEQ ID NO: 1, see page 20, lines 15-23. Edelstein et al. further teach the use of primer sequences that correspond to various regions of the exons of the prostate specific antigen gene.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting PSA expressing cells as taught by Gao et al. to enhance the sensitivity and specificity of detecting PSA using the primers taught by Edelstein et al. for the purpose of reducing the background noise. A person of ordinary skill in the art would have been motivated to combine the method for detecting prostate cancer as taught by Gao et al. by incorporating the step to enhance sensitivity of detection of PSA as taught by Edelstein et al. for the purpose of developing an improved and sensitive system for detecting PSA-expressing cells from a mixture of cells.

One of ordinary skill in the art would have a reasonable expectation of success that the combination of the teachings of Gao et al and Edelstein et al. would provide the advantage of developing a sensitive and an improved system for amplifying target nucleic acid molecules because Edelstein et al. explicitly taught the enhancing sensitivity and specificity of detection of PSA, see page 19, lines 5-18.

Thus, claims 1-6 and 11-16, 18, and 20 are obvious over Gao et al. in view of Edelstein et al.

15. Claims 1, 4-11, 13, 14, 16, and 18, are rejected under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology 53: 714-721, 1999) in view of Terstappen et al. (US Patent 6,365,362, filed 12 February 1999).

The teachings of Gao et al. are described supra.

Gao et al. do not teach isolating epithelial cells using immunological methods. This deficiency is made up for by the teachings of Terstappen et al.

Terstappen et al. teach a method for detection and enrichment of prostate specific cells from blood sample said method comprises use of immunomagnetic beads (dynal magnetic beads) to isolate said cells, see column 8, lines 11-53. Terstappen et al. teach the use of antibodies to epithelial antigens such as anti-EpCAM to enrich or isolate epithelial cells, see column 10, lines 32-37. Terstappen et al. teach the use of p53 as a marker for metastatic potential and aggressiveness, see column 10, lines 19-26.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detecting PSA expressing cells as taught by Gao et al. with enrichment of tumor specific cells as taught by Terstappen et al. for the purpose of amplifying tumor specific cells and reducing the background noise. A person of ordinary skill in the art would have been motivated to combine the method for detecting prostate cancer as taught by Gao et al. by incorporating the step to enriching tumor specific cells as taught by Terstappen et al. for the purpose of developing an improved and sensitive system for detecting PSA-expressing cells from a mixture of cells to reduce background noise.

One of ordinary skill in the art would have a reasonable expectation of success that the teachings of Gao et al and Terstappen et al. would achieve an expected advantage of developing a sensitive and an improved system for amplifying target nucleic acid molecules because Terstappen et al. explicitly taught the enriching circulating tumor specific cells for detection of cancer cells, see column 15, lines 54-67; column 16, lines 1-6.

Thus, claims 1, 4-11, 13, 14, 16, and 18, are obvious over Gao et al. in view of Terstappen et al.

## *Conclusion*

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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**PRIMARY EXAMINER**
amHarris

David Humphrey, Ph.D.

September 12, 2006